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Iron deficiency in cystic fibrosis

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SUMMARY Iron state was measured as part of the comprehensive assessment of 165 patients with cystic fibrosis. Of 127 patients, 41 (32%) had low serum ferritin concentrations and at least this proportion were iron deficiency.

Iron state did not correlate with clinical score, radiological score, or results of sputum culture. There was no evidence that patients with iron deficiency were either in better or worse clinical condition than those with better iron stores.

As survival improves in cystic fibrosis the importance of good nutrition becomes increasingly apparent. Careful attention to details of diet and to dietary supplementation is routine in most cystic fibrosis centres.

Iron supplements are not generally considered necessary and are not usually provided. It is widely believed that individuals with malabsorption secondary to pancreatic insufficiency do not become iron deficient; current paediatric opinion suggests that in cystic fibrosis 'because of the abnormally low pH of the upper jejunum, the absorption of iron is enhanced'.[1] There are similar statements in other paediatric textbooks.[2] In addition, there is concern that iron may encourage bacterial infection.[3]

One hundred and sixty five patients with cystic fibrosis underwent comprehensive assessments of their clinical state in our unit. Their serum ferritin concentrations were compared with their general clinical scores, chest radiograph scores, and the presence of pseudomonas infection. We also report their haematological data.

Methods

Details of the comprehensive assessments of patients with cystic fibrosis performed at this centre have been reported.[4] The relevant results from the first complete assessment for each patient are presented. None of the subjects was receiving iron supplements at the time of assessment.

The assessment included a full history, physical examination, and chest *x* ray films. The Shwachman clinical score[5] and Chrispin-Norman chest *x* ray score[6] were calculated.

Sputum was cultured at the assessment and results of previous cultures obtained. Patients were classified according to whether pseudomonas was grown regularly (Y), had previously been grown intermittently (I), or had never been grown (N).

A fasting blood sample was taken. Haemoglobin and mean corpuscular volume were measured by Coulter counter. Serum ferritin concentration was measured using an in house method, a polyethylene glycol accelerated, post-precipitated, double antibody radioimmunoassay, a modification of the method of Luxton *et al.*[7] The samples were batched for this measurement. Serum ferritin concentrations of less than 12 ng/ml represented reduced or absent iron stores.[8]

Comparison was made with clinical state, changes on chest *x* ray film, and chest infection by calculating Spearman rank correlation coefficients between serum ferritin concentration and Shwachman score, Chrispin-Norman score, and the presence of pseudomonas chest infection, respectively. In view of the progression of the disease with age, the coefficients were calculated separately for each age group.

Table 1 *Serum ferritin concentration by age in the 127 patients with cystic fibrosis studied*

Age in completed years	*Not measured*	*Serum ferritin*	
		≥12 ng/ml	*<12 ng/ml*
0	1	6	1
1, 2	6	16	5
3, 4	4	11	7
5–7	6	10	11
8–10	9	15	7
11–15	6	12	6
16+	6	16	4
Total (No (%))		86 (67·7)	41 (32·3)

Table 2 *Shwachman score, chest x ray score, and presence of pseudomonal chest infection by age in patients with cystic fibrosis*

Age in completed years	*No*	*Shwachman score*		*Chrispin-Norman score*		*Pseudomonas infection*		
		Range	*Median*	*Range*	*Median*	*N*	*I*	*Y*
0	8	70–100	95	0–6	1	8	0	0
1, 2	27	55–100	85	0–9	2	24	1	2
3, 4	22	40–100	85	0–11	3	18	2	2
5–7	27	40–100	80	1–25	7	20	0	7
8–10	31	45–90	75	0–20	7	20	0	11
11–15	24	30–95	72·5	2–27	9	9	4	11
16+	26	40–95	60	3–23	14	11	0	15

N=Pseudomonas absent; I=pseudomonas intermittently grown; Y=pseudomonas present.
For Shwachman score, higher score=better clinical state; for Chrispin-Norman score, higher score=worse chest *x* ray.

Results

There were 78 boys, aged 9 weeks to 25 years 7 months (median 8 years 5 months), and 87 girls, aged 24 weeks to 30 years 2 months (median 8 years). No sex differences emerged for any of the variables studied.

Serum ferritin concentration was less than 12 ng/ml in 41 of the 127 patients studied (32%) (Table 1). These patients were distributed evenly throughout the age range.

Three of 161 patients (2%) had a haemoglobin concentration less than 11 g/dl and 14 (9%) between 11 and 12 g/dl. Mean corpuscular volumes were less than 75 fl in eight (5%) and between 75 and 80 fl in 32 (21%) of 153 patients.

All variables of clinical state gradually worsened with increasing age. The Shwachman score declined, the Chrispin-Norman score rose, and there was an increase in the incidence of pseudomonas chest infection (Table 2). At all ages, however, there were patients whose clinical state was good.

There was no correlation between serum ferritin concentration and Shwachman score, Chrispin-Norman score, or presence of pseudomonas infection.

Discussion

A total of 32% of our patients had low serum ferritin concentrations, a finding that conflicts with generally accepted teaching concerning iron state in cystic fibrosis but that supports the findings of Ater *et al*,[9] 13 of whose 39 patients (33%) had a serum ferritin concentration below 12 ng/ml.

In the assessment of iron deficiency a serum ferritin concentration of less than 12 ng/ml represents reduced or absent iron stores, whatever other complications are present.[8] High serum ferritin concentrations are found in inflammation, common in patients with cystic fibrosis, so that 32% is a minimum estimate of the incidence of poor iron state in patients with cystic fibrosis from Yorkshire.

Many of our patients may well have had a relative anaemia, in view of their poor pulmonary state.[9]

Cystic fibrosis is a serious disease in which premature death is commonly caused by the effects of repeated chest infections. It is almost certain that nutritional problems, which are common, contribute considerably to morbidity and mortality, and it would be logical to attempt to correct deficiencies, possibly including iron deficiency.

There has been much discussion, however, of the relation between iron state and bacterial infection. In vitro, bacteria such as *Escherichia coli* grow and multiply under iron rich conditions,[3] although iron saturation in vivo may not have the same effect on bacterial growth and multiplication.[10] On the other hand, reduced immunological resistance to bacterial infection has been seen in iron deficiency,[3] and in rats iron deficient diets reduce thymic and splenic growth and differentiation.[11]

The relevance of such experimental work to humans is unclear. Catastrophic effects of iron supplementation—namely, lethal bacterial infections—have followed the use of prophylactic parenteral iron in newborns from a population thought to have severely compromised nutrition and to be at risk of multiple deficiencies.[12] Acute pseudomonal pyelonephritis is not enhanced, however, by treatment with iron.[13]

There are indications that mucoid *Pseudomonas aeruginosa* is the most stable strain under iron limited conditions[14] and that emergence of the mucoid strain so common in patients with cystic fibrosis is favoured by iron restricted conditions in the lung.[15]

We found no evidence at any age of a correlation between higher serum ferritin concentration and worse clinical state, more severe chest involvement,

or the presence of pseudomonas chest infection. Neither did we find any correlation between these variables and lower serum ferritin concentration.

Our approach to management is to strive for physiologically 'normal' variables, wherever possible, and our patients receive aggressive dietary management and vitamin supplementation. In view of the conflicting and confusing evidence about iron state, particularly regarding bacterial infection, we propose a trial of iron supplementation for our patients with cystic fibrosis who have iron deficiency.

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